Tris(4-chlorophenyl)methane (TCPMe) and Tris(4chlorophenyl)methanol (TCPMOH)

TCPMe and TCPMOH were nominated by the National Institute of Environmental Health Sciences based on their widespread occurrence and persistence in the environment and limited availability of toxicity data. The NTP's draft research concept includes ADME studies of TCPMe and TCPMOH in rats and mice; uterotrophic and Hershberger assays pending positive *in vitro* results; an *in vivo* micronucleus test; subchronic studies including perinatal exposure to investigate systemic and reproductive toxicity and finally perinatal carcinogenesis and multigeneration continuous breeding reproduction studies to evaluate the long-term effects of TCPMe and TCPMOH. The animals killed as a result of this ambitious research program would number in the thousands, but it is difficult to imagine how any information gained might benefit public health.

It is believed that the source for entry of TCPMe into the environment results from the presence of TCPMe as an impurity in DDT and it has been assumed that TCPMOH is a metabolite of TCPMe. The U.S. Environmental Protection Agency issued a cancellation order for DDT in 1972 based on adverse environmental effects of its use, as well as potential human health risks. Further, the Stockholm Convention on Persistent Organic Pollutants (POPs) bans DDT globally for all uses except for malaria control. The NTP notes in its research concept that TCPMe and TCPMOH have been reported to be used in the production of synthetic high polymers and lightfast dyes for acrylic fibers, and it claims that these uses may also contribute to environmental and occupational exposures. However, the source of these reports appears to be a Chemical Abstracts Search of TCPMOH conducted by Jarman et al. (1992), and these authors concluded that none of the citations they found suggest large-scale industrial production of TCPMOH – they are only certain Japanese and British patent notifications. Further, Buser (1995) questions whether these uses would account for the apparently long-time presence of TCPMOH in the environment in any case.

Since it is very likely that DDT used more than forty years ago constitutes the major – if not the only – source for environmental TCPMe and TCPMOH, and since DDT is now effectively banned world-wide and the subject of large-scale clean-up efforts, how might any information gained from this research program be used to further regulate exposure to TCPMe and TCPMOH? Buser (1995) suggests that analyses of technical DDT from a range of manufacturers could establish that the presence of TCPM as an impurity in DDT or its wastes is the major source for environmental TCPMe. At the very least, such analyses should be performed prior to initiating this animal testing program.

If additional testing is still perceived to be required, we note that uterotrophic and Hershberger assays are proposed if estrogen and androgen receptor binding is observed *in vitro.* While we commend this tiered approach, we emphasize that both receptor binding and transcriptional activation assays should be conducted for evaluating estrogenic and androgenic activities *in vitro*. Also, for genotoxicity, micronuclei evaluation *in vivo* is proposed. Instead, we encourage the use of an *in vitro* micronucleus assay, currently Organisation for Economic Co-operation and Development Test Guideline 487 (draft) in which micronuclei are induced in the cytoplasm of cultured mammalian cells during interphase by both aneugenic and clastogenic substances. In addition, immunochemical labeling of kinetochores or hybridization with general or chromosome-specific centromeric/telomeric probes can give information on the nature and mechanism of formation of micronuclei. The recently updated World Health Organization/International Programme on Chemical Safety Harmonized Scheme for Mutagenicity Testing incorporates this assay as part of its primary screen: substances yielding negative results

are presumed non-mutagenic and no subsequent *in vivo* tests are required (Eastmond DA, et al. 2009).

References

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